

ARAVA™

Leflunomide

Hoechst Marion Roussel, Inc.

FDA Arthritis Advisory Committee

August 7, 1998

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ARAVA

- Disease-controlling anti-rheumatic drug
- Pyrimidine synthesis inhibitor
- Anti-proliferative effects
- Immunomodulatory agent
- Developed specifically for RA

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Impact of Rheumatoid Arthritis

- Prevalence: over 2 million patients
- Direct medical costs: 3X those without RA
- Income loss: \$5-6 billion/year

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Goals of Treatment of Rheumatoid Arthritis

- Improve signs and symptoms of disease
- Retard joint destruction by slowing disease progression
- Improve function and health-related quality of life

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Regulatory History of ARAVA

- FDA/Sponsor interactions
- NDA submitted March 98
- Priority review requested based on
 - Meaningful therapeutic benefit for patients with high unmet medical need
 - Retardation of disease progression
 - Improvement in health-related quality of life
- Priority review granted April 98

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Agenda

- Introduction - Elaine Waller, PharmD
- Preclinical and Pharmacokinetic Data
 - Mark Eller, PhD
- Clinical Efficacy Data - Vibeke Strand, MD
- Clinical Safety Data - Iris Loew-Friedrich, MD
- Clinical Evaluation of Arava
 - Marc Hochberg, MD
- Conclusion - Elaine Waller, PharmD

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Agenda

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Leflunomide

- Pharmacology
- Toxicology
- Pharmacokinetics

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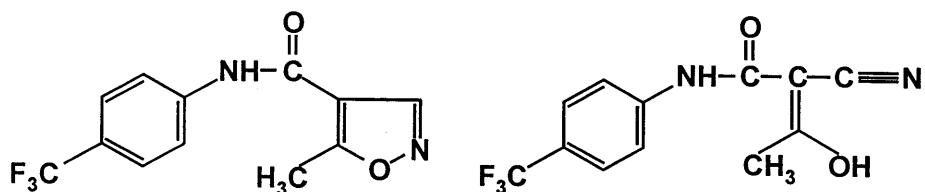
Leflunomide

- Pharmacology
- Toxicology
- Pharmacokinetics

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Leflunomide and Active Metabolite



Leflunomide

A77 1726
Active Metabolite

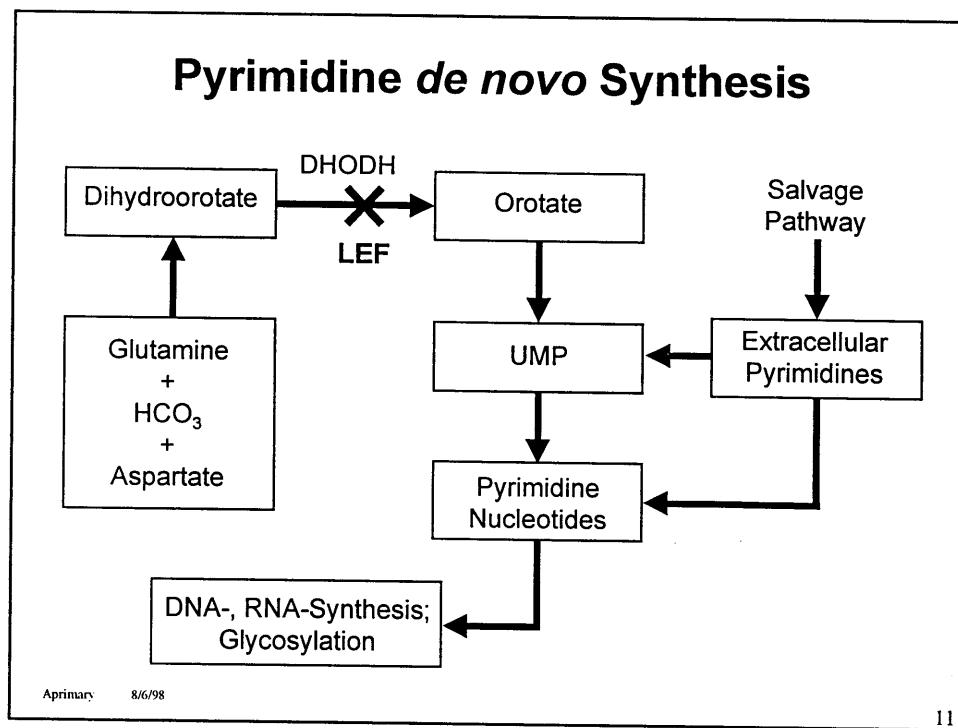
Inhibition of:

- Clonal expansion of T-cells
- De-Novo pyrimidine synthesis
- Dihydroorotate dehydrogenase (DHODH)

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Pyrimidine *de novo* Synthesis



Nucleotide *de novo* Synthesis in Lymphocytes

Activation

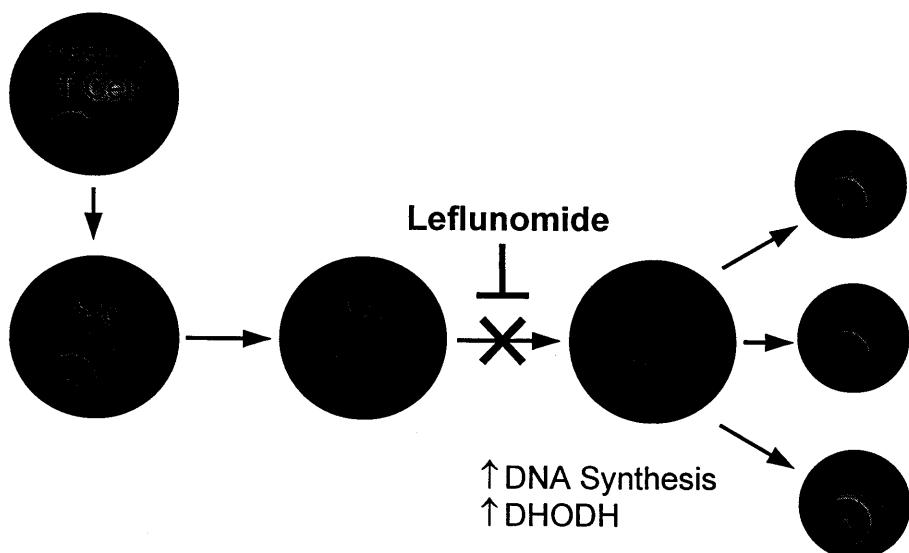
Purines

2 x

Pyrimidines

7- 8 x

Leflunomide Blocks T Cell Clonal Expansion



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Leflunomide Activity

Species	IC ₅₀ DHODH Inhibition (nM Active Metabolite)	IC ₅₀ Anti-Proliferative Activity (μM Active Metabolite)
Rat	16 (1x)	0.14 (1x)
Mouse	81 (5x)	16 (114x)
Human	657 (40x)	46 (328x)

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Leflunomide in Models of Human Autoimmune Diseases

- Rheumatoid arthritis
 - Adjuvant arthritis of rat
 - Collagen type II arthritis
 - Proteoglycan polyarthritis
- Other disease models

Leflunomide Pharmacology Summary

Molecular specificity	Selective inhibition of a key biosynthetic pathway
Cellular selectivity	Targets cells that crucially depend on <i>de novo</i> pyrimidine synthesis
Therapeutic effect	Control of the autoimmune response

Leflunomide

- Pharmacology
- Toxicology
- Pharmacokinetics

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Leflunomide

- Repeated-dose toxicity
(mouse, rat, dog, monkey)
- Reproductive toxicity
 - Mutagenicity
 - Carcinogenicity

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Repeated-Dose Toxicity

Dose-Related Direct Effects

- Related to DHODH inhibition
 - Bone marrow and blood
 - Gastrointestinal tract
 - Spleen
 - Thymus
 - Lymph nodes
 - Skin
 - Liver

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Repeated-Dose Toxicity (Cont'd)

Dose-Related Indirect Effects

- Related to immunosuppressive effects
 - Heart
 - Liver
 - Lungs

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Reproductive Toxicity

- Consistent with anti-proliferative activity of Leflunomide
 - Atrophy of reproductive organs in rats, mice and dogs
 - Embryotoxicity in rats and rabbits (retardation, embryolethality)
 - Teratogenicity in rats and rabbits (malformations of head, rump, vertebral column, ribs and limbs)
- NOEL in rats and rabbits: 1 mg/kg

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Mutagenicity

- No genotoxic/mutagenic potential in *in vitro* assays:
 - Ames, HGPRT, UDS
- No genotoxic/mutagenic potential in *in vivo* assays:
 - Micronucleus test (mouse), chromosomal aberration (Chinese hamster)
- Trace metabolite, TFMA, + *in vitro*, - *in vivo*

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Carcinogenicity

- No carcinogenic effects observed in rats
- Increased incidence of lymphomas and lung tumors in mice are a probable consequence of dose related immunosuppression

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Safety Margin

Leflunomide Active Metabolite

AUC (rat NOEL): 9.16 µg•h/mL	AUC (human): 1,000 µg•h/mL
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Methotrexate

AUC (rat LOEL): 33 ng•h/mL	AUC (human): 1,230 ng•h/mL
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Safety Margin

Species	IC ₅₀ DHODH Inhibition (nM Active Metabolite)	IC ₅₀ Anti-Proliferative Activity (μM Active Metabolite)
Rat	16 (1x)	0.14 (1x)
Mouse	81 (5x)	16 (114x)
Human	657 (40x)	46 (328x)

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Toxicology Summary

- Toxicity, carcinogenicity and reproductive toxicity consistent with anti-proliferative and immunosuppressive activity
- No safety margins can be calculated based on plasma levels (same as with MTX)
- Significant species differences (DHODH, anti-proliferative activity)

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Leflunomide

- Pharmacology
- Toxicology
- **Pharmacokinetics**

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Leflunomide PK Well Characterized

- Healthy men and women
- RA patients, including population pharmacokinetics
- Renal patients
- Single and multiple doses
- Interaction studies
 - Food, cholestyramine, oral contraceptives, methotrexate, cimetidine, rifampin, warfarin

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Pharmacokinetic Properties

Well Absorbed

- Bioavailability of tablets relative to an oral solution is 80%
- No food effect

Pharmacokinetic Properties

Extensive Metabolism

- Nearly complete first pass conversion to a primary active metabolite
- Several minor metabolites, multiple enzyme systems

Pharmacokinetic Properties

Long Elimination Half-Life

- Half-life of active metabolite is 2-4 weeks
- Loading dose is required
- Activated charcoal or cholestyramine can dramatically speed elimination

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Pharmacokinetic Properties

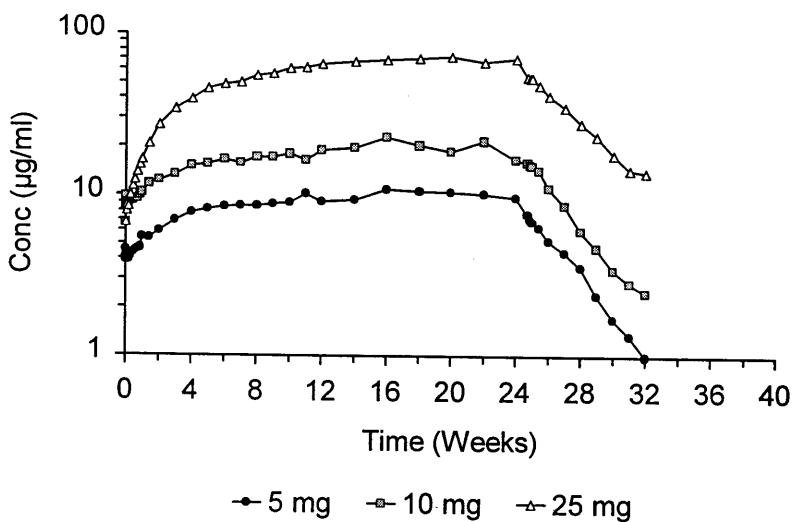
Linear Pharmacokinetics

- Change in dose leads to a proportional change in plasma levels

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Active Metabolite Pharmacokinetics in RA Patients After 5, 10, and 25 mg Leflunomide Daily for 24 Weeks



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Pharmacokinetic Properties

Highly Protein Bound

- Free fraction < 2%
- Independent of concentration
- Not significantly removed by dialysis
- Does not displace, is not displaced by warfarin

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Pharmacokinetic Properties

Drug Interactions

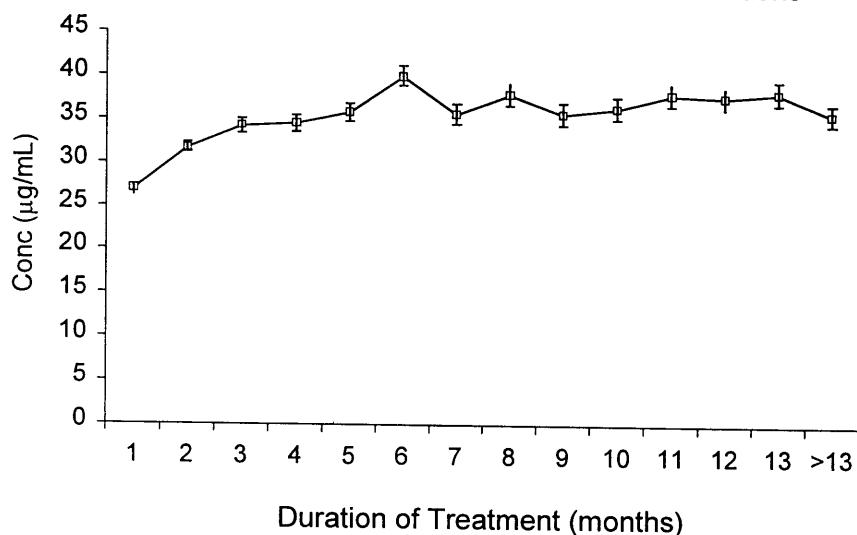
- No interaction with oral contraceptives, MTX, rifampin or cimetidine
 - *In vitro* studies suggest that the active metabolite may inhibit CYP2C9 mediated metabolism (eg diclofenac).
- No differences in safety and efficacy profiles.

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Pharmacokinetic Properties

Population PK: mean active metabolite concentrations



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Pharmacokinetic Properties

Population PK

- PK parameters from Phase III studies

Parameter	Mean ± SD
Clearance (mL/hr)	28.9 ± 17.3
Volume of distribution (L)	11.8 ± 3.7
Half-life (days)	16.2 ± 11.0

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Pharmacokinetic Properties

Population PK

- No sub-groups requiring different dose
- Clearance 38% higher in smokers
- Clearance 20% higher in males
- No effect of age
- No drug interactions (except cholestyramine)

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Pharmacokinetic Summary

- Well absorbed
- Extensive metabolism: active metabolite
- Long elimination half-life
- Dose proportional pharmacokinetics
- High plasma protein binding
- No clinically important drug interactions
(except cholestyramine)

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Preclinical and Pharmacokinetic Summary

Pharmacology, toxicology and pharmacokinetics have been well characterized

- Immunomodulatory mechanism of action is based on DHODH inhibition
- Animal toxicity is consistent with antiproliferative activity and immunosuppression
- Pharmacokinetics principally determined by long half-life of active metabolite

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Efficacy Results

- **Pivotal Studies Design**
- Patient Population and Disposition
- Signs and Symptoms
- X-Ray Analysis
- Function / HRQOL
- Summary

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Phase III Clinical Trials

Agent/Dose	301US	301MN	302MN
LEF Dose	100 mg x 3 days loading followed by 20 mg/day		
Design	RCT	RCT	RCT
N	482		
Control	Placebo MTX: 7.5 mg/wk; or ↑ 15 mg/wk, wks 6 to 9 for active disease		
Duration	12 mos		
Blinded			
Placebo Switch	On or after 4 mos		
Countries	US, Canada		

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Phase III Clinical Trials

Agent/Dose	301US	301MN	302MN
LEF Dose	100 mg x 3 days loading followed by 20 mg/day		
Design	RCT	RCT	RCT
N	482	358	
Control	Placebo MTX: 7.5 mg/wk; or ↑ 15 mg/wk, wks 6 to 9 for active disease	Placebo SSZ: 0.5→2 g/d	
Duration	12 mos	6→12 mos	
Blinded			
Placebo Switch	On or after 4 mos	At 6 mos	
Countries	US, Canada	EU, SA, AUS	

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Phase III Clinical Trials

Agent/Dose	301US	301MN	302MN
LEF Dose	100 mg x 3 days loading followed by 20 mg/day		
Design	RCT	RCT	RCT
N	482	358	999
Control	Placebo MTX: 7.5 mg/wk; or ↑ 15 mg/wk, wks 6 to 9 for active disease	Placebo SSZ: 0.5→2 g/d	MTX: 7.5→10 mg/wk; or 15 mg/wk on/after 12 wks at PI discretion
Duration	12 mos	6→12 mos	12 mos
Blinded			
Placebo Switch	On or after 4 mos	At 6 mos	
Countries	US, Canada	EU, SA, AUS	EU, SA

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Efficacy Results

- Pivotal Studies Design
- **Patient Population and Disposition**
- Signs and Symptoms
- X-Ray Analysis
- Function / HRQOL
- Summary

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Demographics

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
Mean Age	54	55	53	58	59	59	58	58
% Female	73	70	75	76	75	69	71	71
Mean Disease Duration (yrs)	7.0	6.9	6.5	7.6	5.7	7.4	3.7	3.8
≤ 2 Years (%)	39	33	40	38	45	42	44	43

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Demographics

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
% RF+ at Baseline	65	60	60	76	83	76	74	76
Mean # DMARDs	0.8	0.9	0.9	1.2	0.9	1.0	1.1	1.1
No Prior DMARD (%)	44	40	44	40	53	51	34	33

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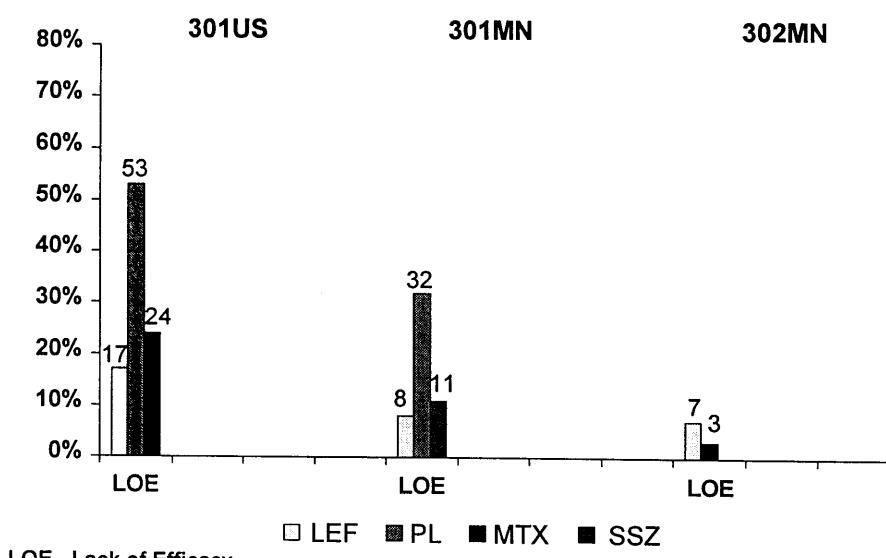
Concomitant Medications

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
NSAIDs (%)	75	65	70	86	87	78	80	87
Steroids (%)	54	55	53	45	45	46	49	45
Folic Acid (%)	97	96	98	0	0	0	8	11

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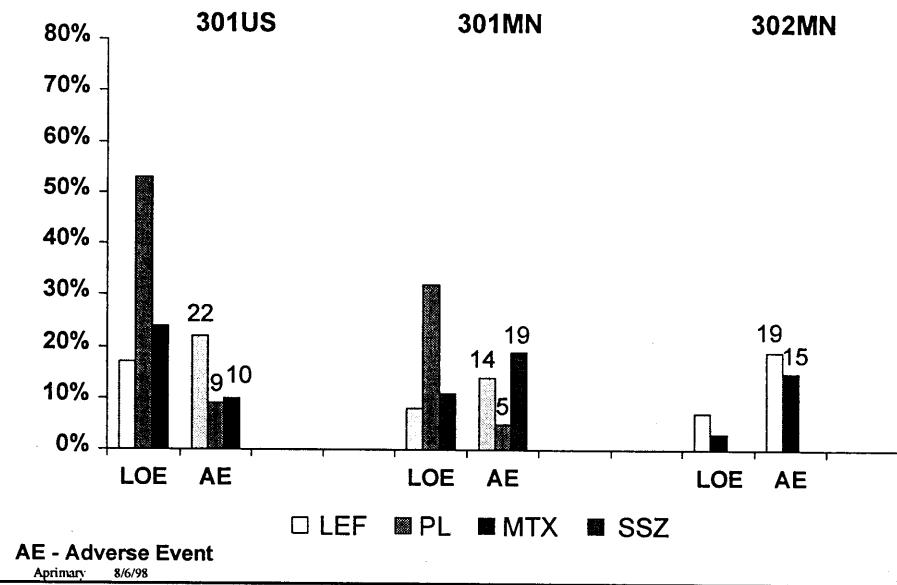
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Patient Disposition - Treatment Withdrawals



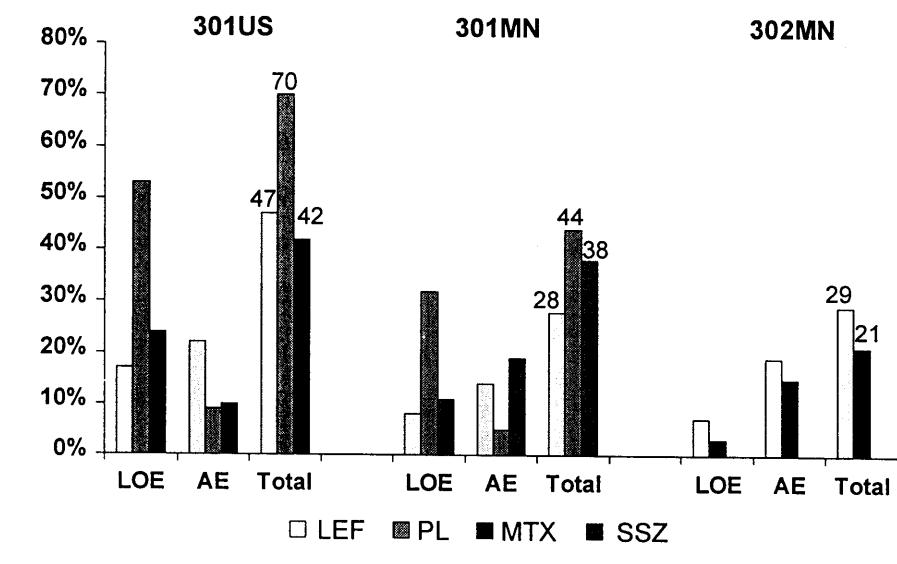
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Patient Disposition - Treatment Withdrawals



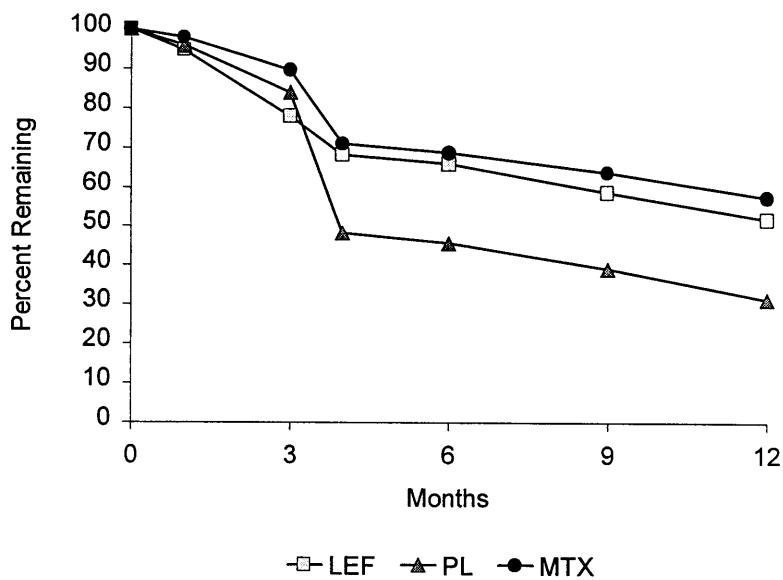
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Patient Disposition - Treatment Withdrawals



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Withdrawals - Kaplan-Meier Analysis - 301US



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Alternate Therapy: 301US

	LEF (182)	PL (118)	MTX (182)
Completed Initial Rx (%)	53	31	58
Alternate Rx (%)			
Eligible	16	51	23
Entered	13	43	18
Total Treated (%)	66	74	76

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Dose Adjustments - MTX Dose Increase

	301US			302MN	
	LEF	PL	MTX	LEF	MTX
Initial MTX Dose	-	-	7.5	-	7.5→10mg at wk 8
↑ MTX to 15 mg/wk (or MTX PL) (%)	(53)	(70)	60 ¹	(54)	53 ²

¹ ↑ Weeks 6-9
² ↑ On or after week 12

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Dose Adjustments for Tolerability

	301US			301MN			302MN	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
Dose decrease (%)	2	0	2	3	3	7	7	18

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Efficacy Results

- Pivotal Studies Design
- Patient Population and Disposition
- **Signs and Symptoms**
- X-Ray Analysis
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ACR Responder

≥ 20% improvement in:

- Tender joint count
- Swollen joint count

and 3 of the following 5:

- Patient global
- MD global
- Pain (VAS)
- MHAQ
- ESR or CRP

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Efficacy Analysis

- Pre-specified primary endpoint: ACR success
 - Completed protocol and ACR responder at endpoint
- Intent to treat
 - All subjects who received one or more doses of study medication and had one or more follow-up evaluations

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Treatment Comparisons

- Primary Comparison
 - Leflunomide vs placebo to determine statistically significant differences
- Secondary Comparisons
 - Leflunomide vs active comparators by confidence intervals to determine statistical equivalence

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Efficacy Overview: Signs and Symptoms

301US and 301 MN

In each trial Leflunomide was clinically and statistically significantly superior to placebo in all measures

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Efficacy Overview: Signs and Symptoms

301US

Leflunomide was clinically and statistically equivalent to methotrexate

301MN

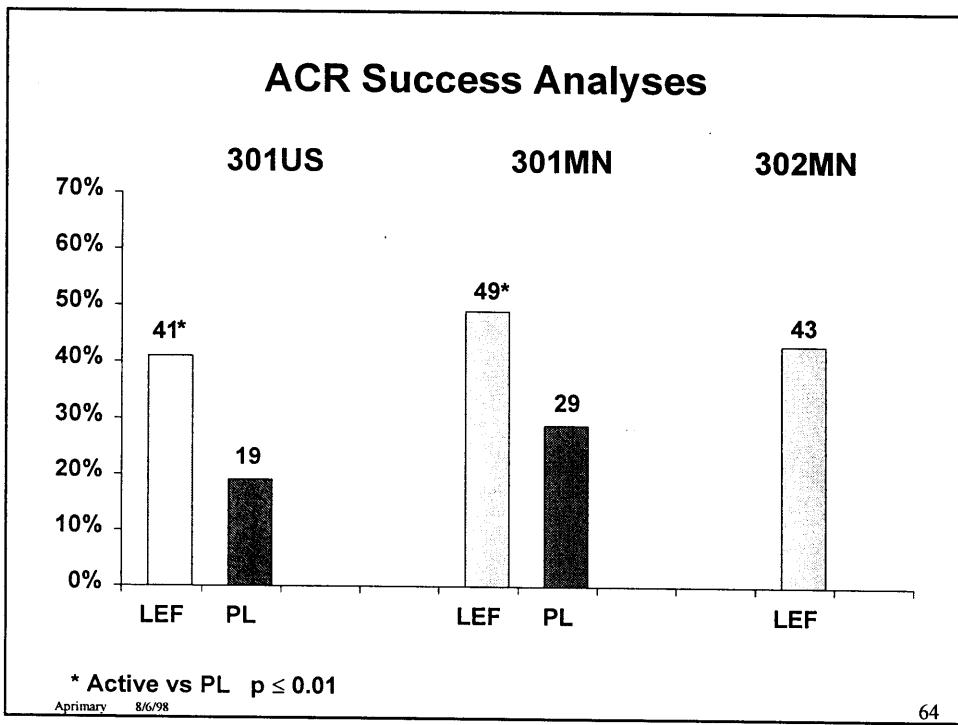
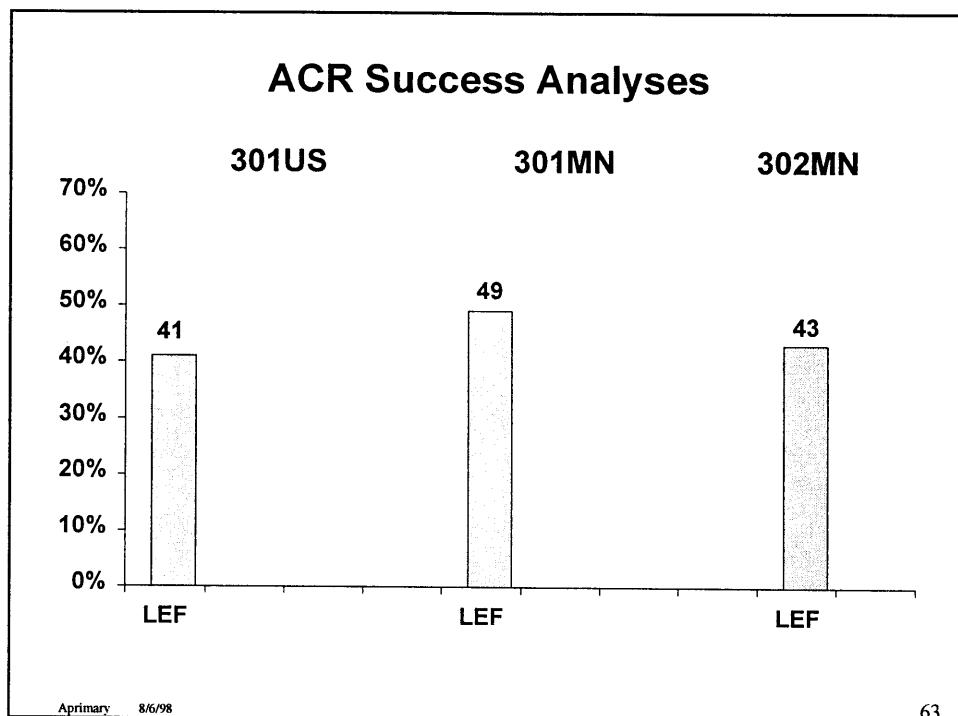
Leflunomide was clinically and statistically equivalent to sulfasalazine

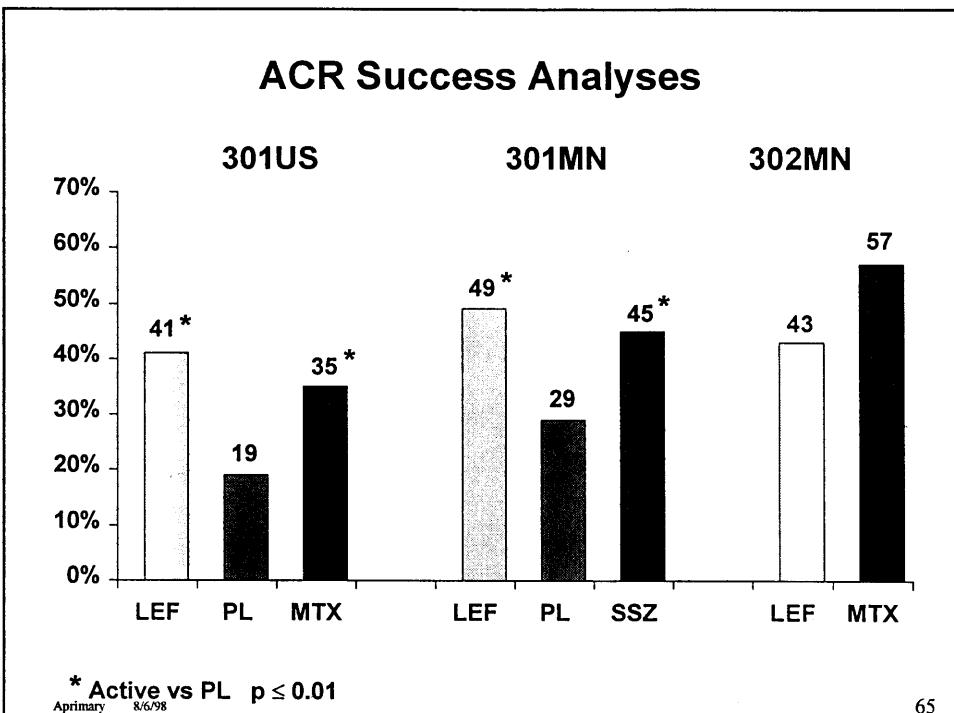
302MN

Methotrexate was statistically superior to leflunomide

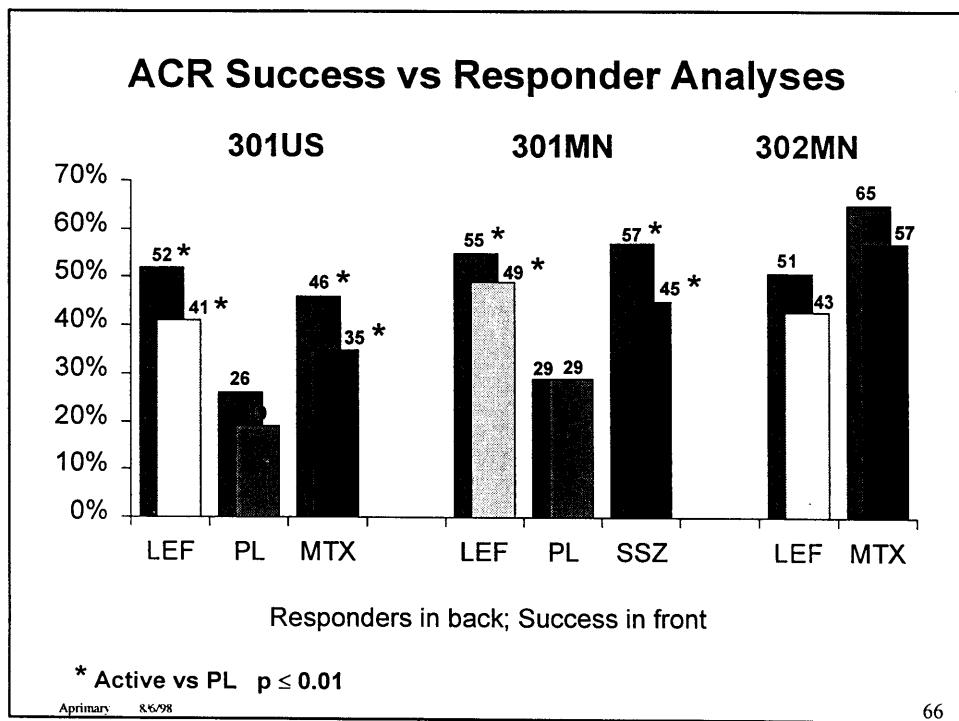
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Percent ACR Success and Responders at Endpoint

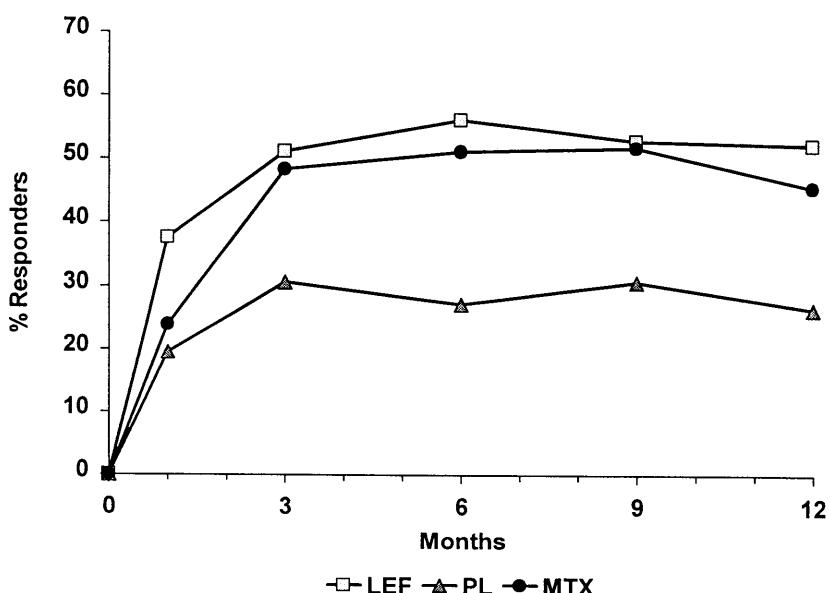
	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
Success	41 *	19	35 *	49 *	29	45 *	43	57
ACR Response (≥20%)	52 *	26	46 *	55 *	29	57 *	51	65
ACR Response (≥50%)	34 *	8	23 *	33 *	14	30 *	31	44

* Active vs PL p≤ 0.01

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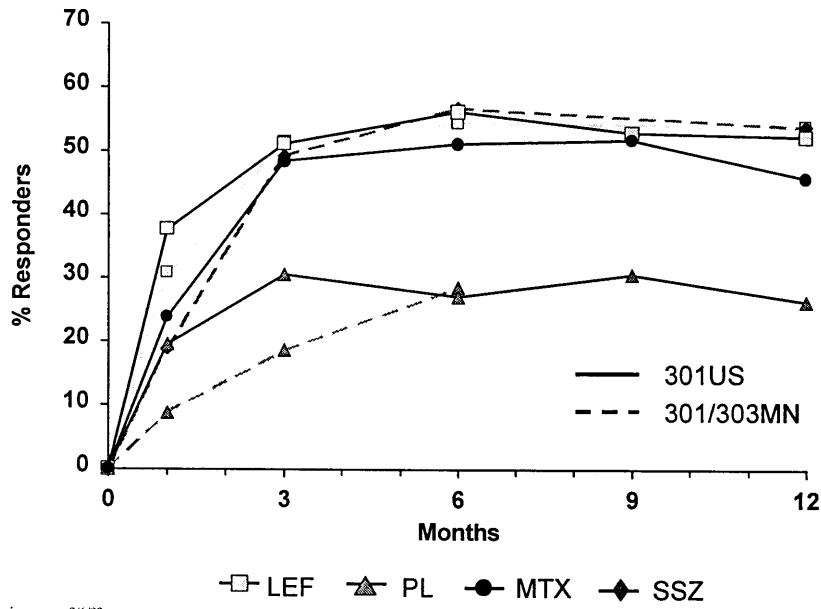
ACR Responders Over Time – 301US



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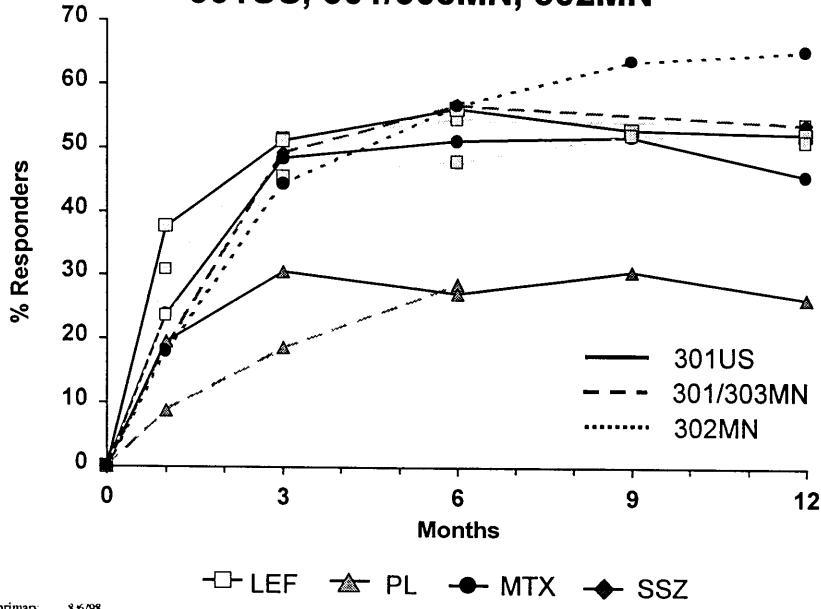
ACR Responders Over Time - 301US & 301/303MN



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ACR Responders Over Time 301US, 301/303MN, 302MN



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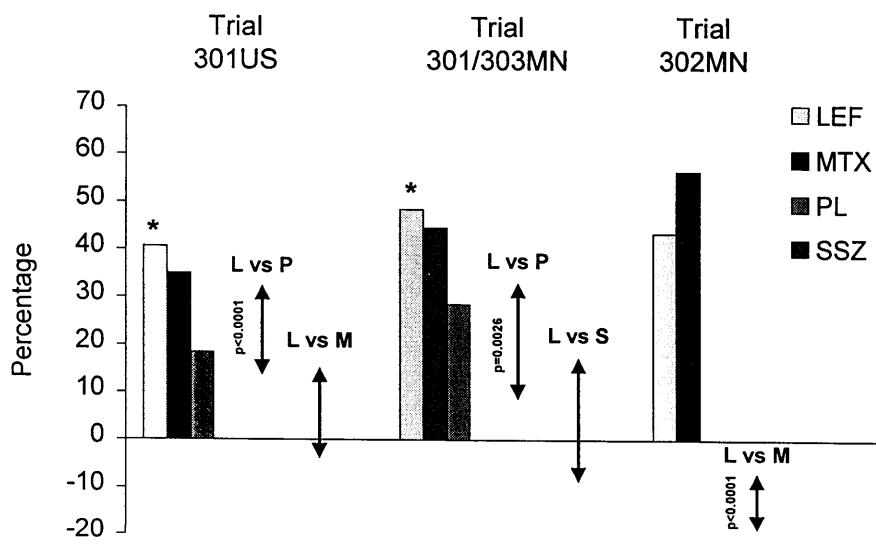
AUC and Response Analyses

Weeks	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
Mean AUC	23.7 *	12.6	22.7 †	11.8 *	5.5	10.5 †	23.0	25.4
Time to:								
Initial Response	8.5	10.4	9.5	7.3	10.0	8.3	10.6	14.4
Sustained Response	10.7	14.7	14.0	7.3	9.7	8.3	9.3	11.2
* LEF vs PL $p \leq 0.01$								
† Active comparator vs PL $p \leq 0.01$								

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% ACR Success



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Efficacy Results

- Pivotal Studies Design
- Patient Population and Disposition
- Signs and Symptoms
- **X-Ray Analysis**
- Function / HRQOL
- Summary

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X-Ray Methodology

- Sharp method
- Fine detail films of hands and feet
- Cassettes and films provided
 - Fine grain
 - Single emulsion
- Investigators trained

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X-Ray Methodology (Cont'd)

- Initial films screened for QC and repeated if necessary
- All films read by Dr. Sharp
 - In patient sets of 2 or 3
 - Randomized and blinded to time sequence

Analysis of X-Ray Data

- Sharp method: 34-36 joints in the hands, 12 in the feet
- Total Sharp score = sum of erosions + joint space narrowing
- X-rays at baseline and endpoint in all studies
- 12 month ITT in 301US
- Sensitivity analysis to account for early withdrawals

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Missing X-Ray Data by Protocol

% Missing	301US	301MN	302MN
LEF	28	32	39
PL	30	32	-
MTX	23	-	32
SSZ	-	36	-

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Total Sharp Score at Baseline

	301US			301MN			302MN	
	LEF (131)	PL (83)	MTX (138)	LEF (89)	PL (62)	SSZ (85)	LEF (304)	MTX (331)
Total Sharp Score	23.11	25.37	22.76	46.26	46.18	41.86	24.94	24.60
Mean Disease Duration (yrs)	7.0	6.9	6.5	7.6	5.7	7.4	3.7	3.8
Predicted Yearly Progression	3.30	3.68	3.50	6.09	8.10	5.65	6.74	6.47

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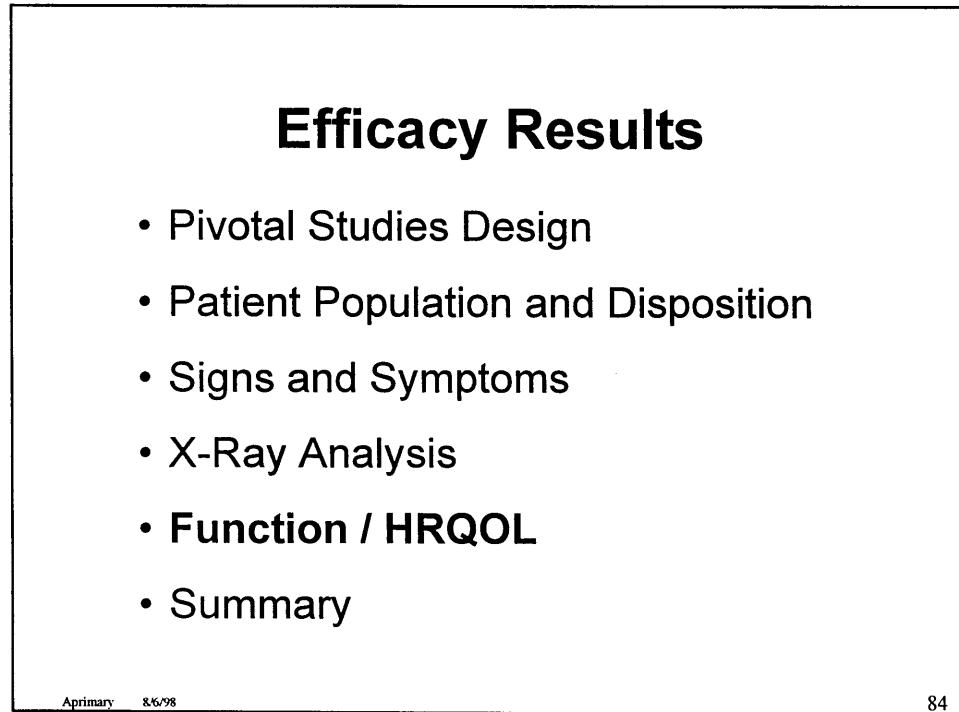
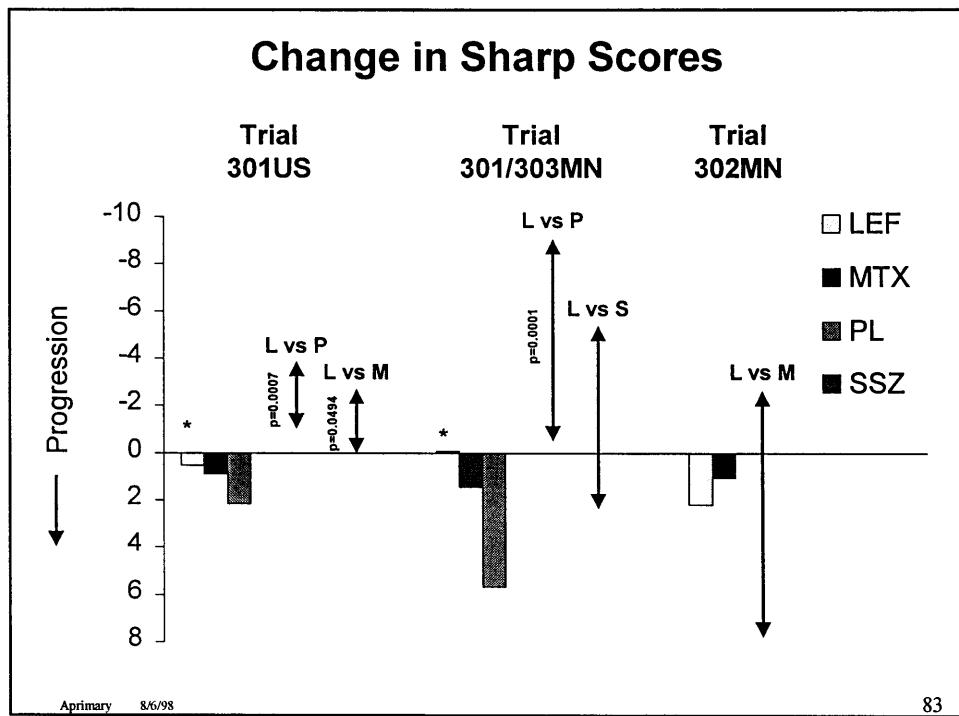
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Change in Total Sharp Scores

	301US			301MN (6 mos)			302MN	
	LEF (131)	PL (83)	MTX (138)	LEF (89)	PL (62)	SSZ (85)	LEF (304)	MTX (331)
Total Score								
Baseline	23.11	25.37	22.76	46.26	46.18	41.86	24.94	24.60
Endpoint	23.63	29.05	23.64	46.20	51.78	43.30	27.13	25.64
Observed Progression	0.53 *‡	2.16	0.88 *	-0.06 *	5.60	1.44 *	2.19	1.04
Predicted Progression	3.30	3.68	3.50	3.05	4.05	2.85	6.74	6.47

* Active vs PL p ≤ 0.01
 ‡ Not statistically equivalent vs MTX

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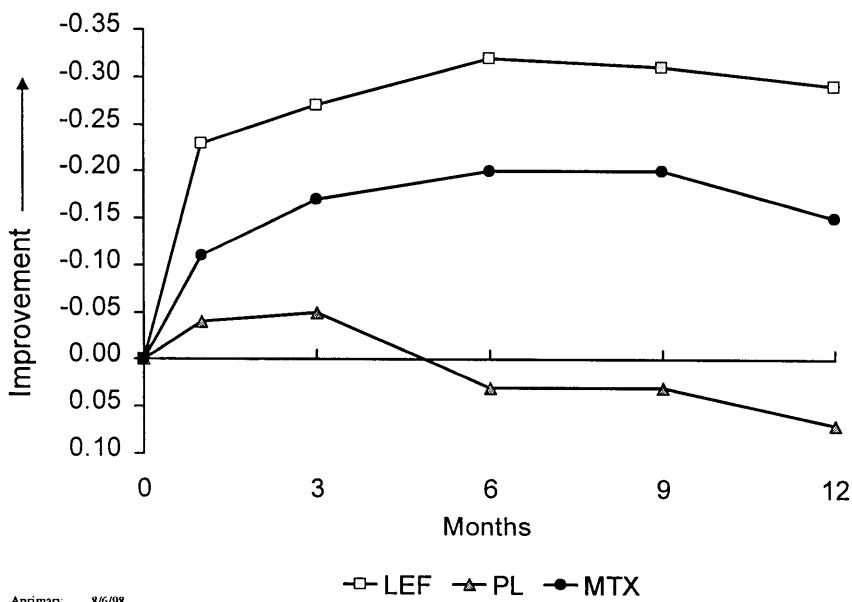
Comparison of Function and Health-Related QOL Instruments

Activities Assessed	MHAQ	HAQ	SF-36
Walking	x	x	x
Climbing Steps		x	x
Reaching	x	x	
Getting in and out of a car	x	x	
Arising	x	x	
Reaching over head		x	
Gripping	x	x	
Eating	x	x	x
Self care ADLs			
Hygiene	x	x	
Dressing, grooming	x	x	x
Instrumental Activities			x
Discretionary activities			
Walking > 1 mile			x
Climbing several sets of stairs			x
Moderate activities			x
Vigorous activities			x

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Mean MHAQ Over Time – 301US



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Change in MHAQ Scores

	301US			301MN			302MN	
	LEF (178)	PL (118)	MTX (179)	LEF (116)	PL (81)	SSZ (113)	LEF (477)	MTX (470)
Baseline	0.78	0.87	0.79	1.14	1.09	0.98	1.08	1.06
Mean Δ	-0.29*‡	0.07	-0.15	-0.50*	-0.04	-0.29	-0.37	-0.44

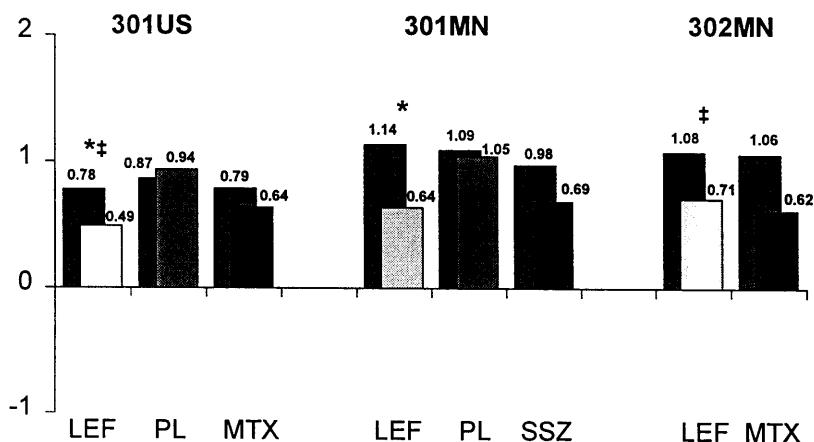
* LEF vs PL p ≤ 0.0001

‡ Indicates LEF and the active comparator were not statistically equivalent

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Improvement in MHAQ Scores



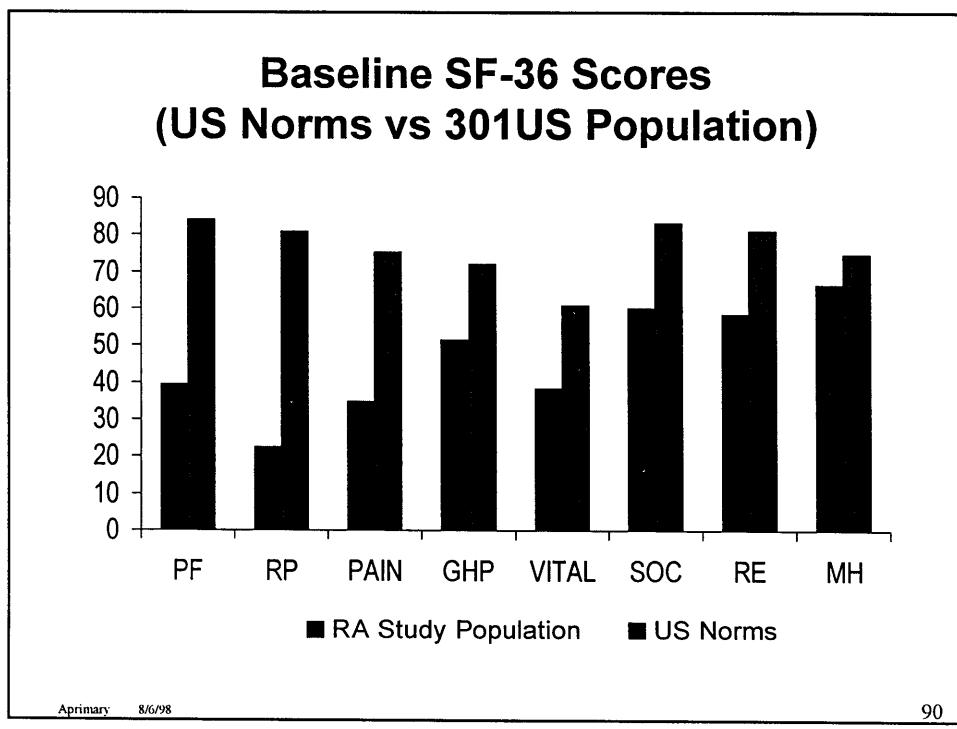
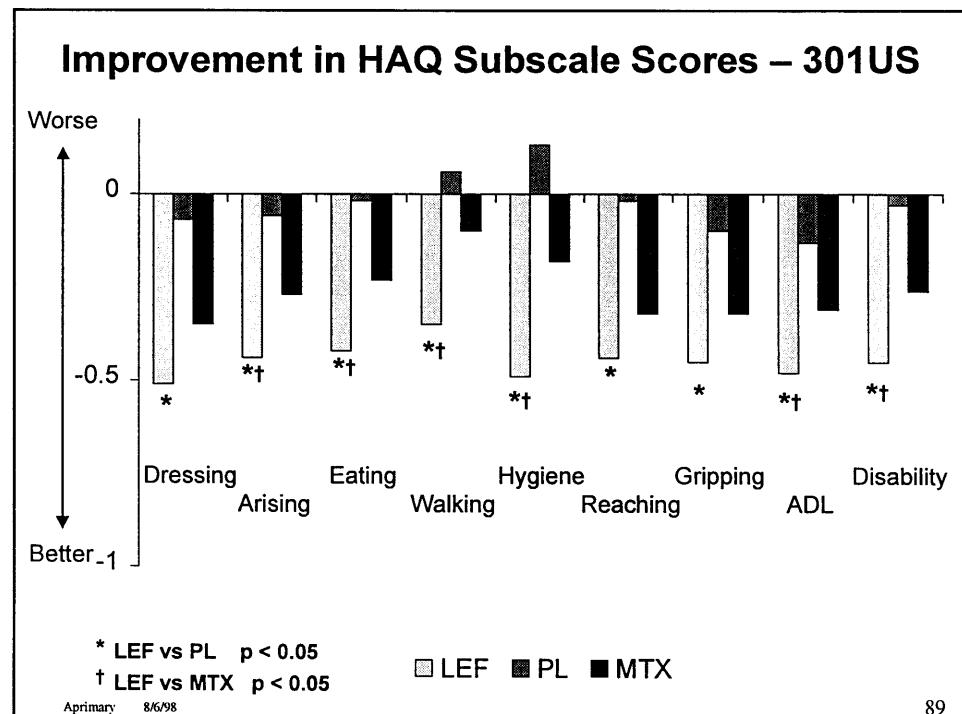
Baseline MHAQ in back; Endpoint MHAQ in front

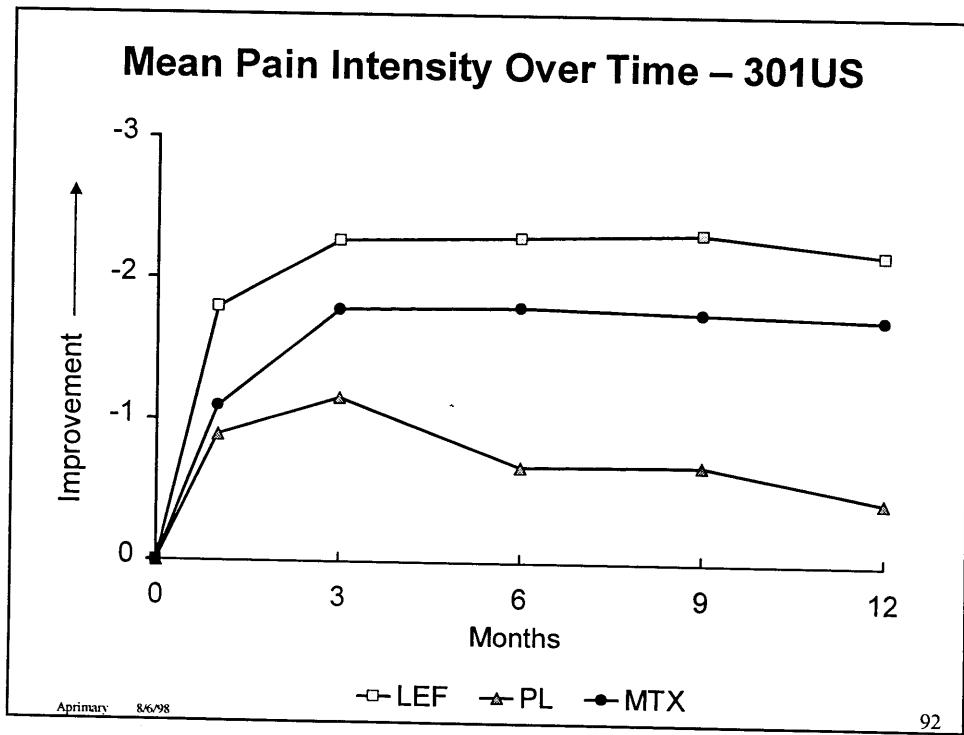
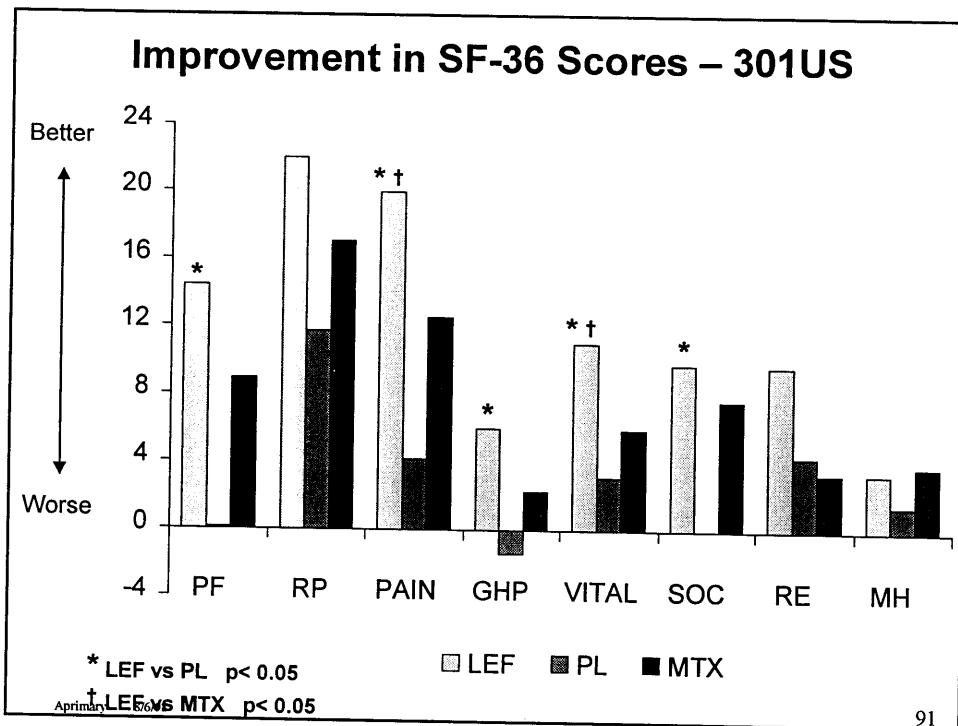
* LEF vs PL p ≤ 0.0001

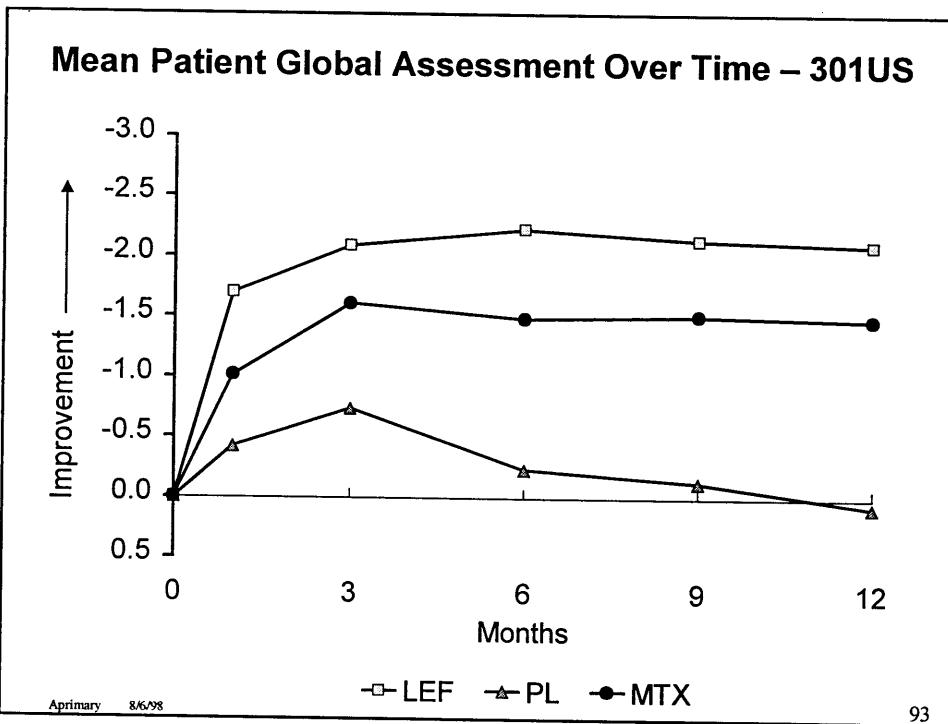
‡ Indicates LEF and the active comparator were not statistically equivalent

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Mean Changes in Function and HRQOL Scores – 301US

With MHAQ (n) =		LEF (166) (178)	PL (101) (118)	MTX (169) (179)
MHAQ	BL:	0.78	0.89	0.79
	Mean Δ :	-0.29 *†	0.07	-0.15
HAQ DI	BL:	1.3	1.3	1.3
	Mean Δ:	-0.45 *†	-0.03	-0.26
PET Top 5	BL:	21.2	22.4	20.4
	Mean Δ:	-6.9 *†	-0.66	-3.41
SF-36 Physical Component	BL:	30.0	28.9	29.7
	Mean Δ:	7.6 *†	1.0	4.6
Work Productivity	BL:	53.3	52.9	51.9
	Mean Δ :	9.8 *	0.3	7.5

* LEF vs PL p ≤ 0.01 † LEF vs MTX p ≤ 0.01

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Efficacy Results

- Pivotal Studies Design
- Patient Population and Disposition
- Signs and Symptoms
- X-Ray Analysis
- Function / HRQOL
- **Summary**

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Efficacy Summary - Signs and Symptoms

Leflunomide is:

- Clinically and statistically superior to placebo in reducing the signs and symptoms of RA
- Clinically and statistically equivalent to SSZ and MTX in 301US and 301MN
- Statistically equivalent to MTX by AUC analysis of ACR response and total Sharp score in 302MN although not statistically equivalent by ACR success analysis

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Efficacy Summary - Disease Progression

Measured by X-Ray, Leflunomide is:

- Significantly superior to placebo in retarding disease progression at 6 and 12 months

Efficacy Summary - Function / HRQOL

Leflunomide:

- Improves function and prevents disability; evident at 6 months and sustained over 12 months
- Is clinically and statistically superior to placebo in improvement in function, performance of physical activities important to the patient, and HRQOL

Agenda

- Introduction - Elaine Waller, PharmD
- Preclinical and Pharmacokinetic Data
 - Mark Eller, PhD
- Clinical Efficacy Data - Vibeke Strand, MD
- **Clinical Safety Data - Iris Loew-Friedrich, MD**
- Clinical Evaluation of Arava
 - Marc Hochberg, MD
- Conclusion - Elaine Waller, PharmD

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Safety Results

- **Exposure**
- Adverse Events
- Serious Adverse Events
- Laboratory
- Summary

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Leflunomide Safety Analysis Databases

- All treated RA patients: n=1339
 - All phase II and phase III studies
- Placebo-Control phase III studies: n=315
 - 301US (active control: MTX) and 301MN (active control: SSZ)
- Active-Control phase III study: n=501
 - 302MN (active control: MTX)

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Phase III Clinical Trials: Patient Numbers

	LEF	PL	SSZ	MTX	Totals
Placebo-Control					
301US	182	118	0	182	482
301MN	133	92	133	0	358
Totals	315	210	133	182	840
Active-Control					
302MN	501	0	0	498	999
Overall Totals	816	210	133	680	1839

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Summary of Drug Exposure in RA Patients in Phase II and III

	Exposed	\geq 6 Months	\geq 12 Months	Patient Years
LEF	1339	1011	838	2077
MTX	680	549	497	936
SSZ	133	76	23	258
PL	310	141	38	226

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Most Common Concomitant Diseases

% With Disease	Placebo-Control				Active-Control	
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)
Hypertension	25.7	25.7	24.1	20.9	21.4	20.5
Hypothyroidism	8.9	5.2	6.0	8.2	4.6	3.4
Depressive disorder	8.6	3.8	0.8	13.7	2.4	3.2
Obesity	7.9	5.7	0	19.2	2.8	2.0
Lipid disorder	6.0	8.1	3.0	9.9	2.8	2.8
Diabetes	5.1	7.6	5.3	4.9	5.2	4.8
Osteoarthritis	4.4	8.1	4.5	13.7	4.6	5.0

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Safety Results

- Exposure
- Adverse Events
- Serious Adverse Events
- Laboratory
- Summary

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Most Common Adverse Events (>5%)

	Placebo-Control				Active-Control		All
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)	LEF (1339)
Body as a whole							
Accidental injury	7.0	5.2	3.0	11.0	6.4	6.8	4.9
Asthenia	6.3	3.8	5.3	5.5	2.6	3.2	3.2
Back pain	6.3	3.3	3.8	8.8	7.6	6.8	4.9
Abdominal pain	5.1	3.8	3.8	7.7	5.8	3.8	5.5
Cardiovascular system							
Hypertension	8.9	4.3	3.8	2.7	9.8	4.0	10.3

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Most Common Adverse Events (>5%) Cont'd

	Placebo-Control				Active-Control		All
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)	LEF (1339)
Gastrointestinal system							
Diarrhea	26.7	11.9	9.8	19.2	22.2	10.0	17.0
Nausea	13.0	11.0	18.8	18.1	12.8	18.1	9.3
Dyspepsia	10.2	10.0	9.0	13.2	5.8	7.0	4.9
Elevated LFT	10.2	2.4	3.8	10.4	5.8	16.9	4.9
GI pain/ Abd. pain	5.7	4.3	6.8	8.2	8.0	7.6	4.6
Vomiting	5.1	4.3	3.8	2.7	3.2	3.4	2.8

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Most Common Adverse Events (>5%) Cont'd

	Placebo-Control				Active-Control		All
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)	LEF (1339)
CNS							
Headache	13.3	11.4	12.0	20.9	9.6	7.8	6.8
Dizziness	5.1	3.3	6.0	4.9	7.0	6.2	4.2
Respiratory system							
Resp. infection	21.0	20.5	20.3	31.9	26.5	24.5	15.1
Bronchitis	5.1	1.9	3.8	6.6	8.0	6.8	6.5
Skin							
Rash	12.4	6.7	10.5	8.8	10.8	9.6	9.9
Alopecia	8.9	1.4	6.0	6.0	16.2	9.8	9.7

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Adverse Events of Potential Clinical Significance

- Gastrointestinal
- Allergic Reactions
- Infections
- Hypertension
- Alopecia

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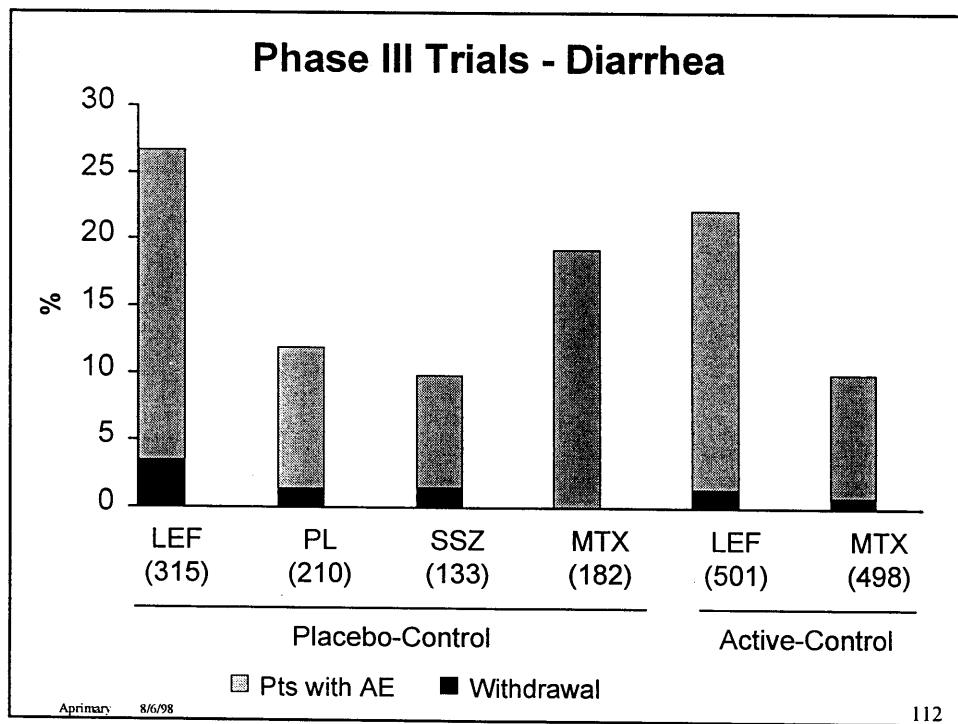
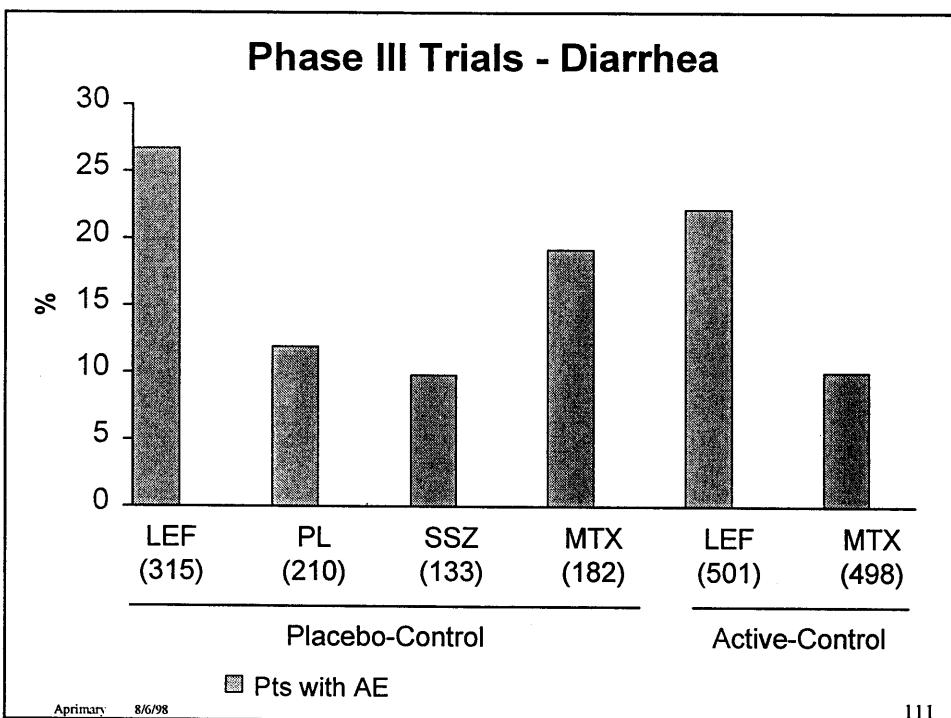
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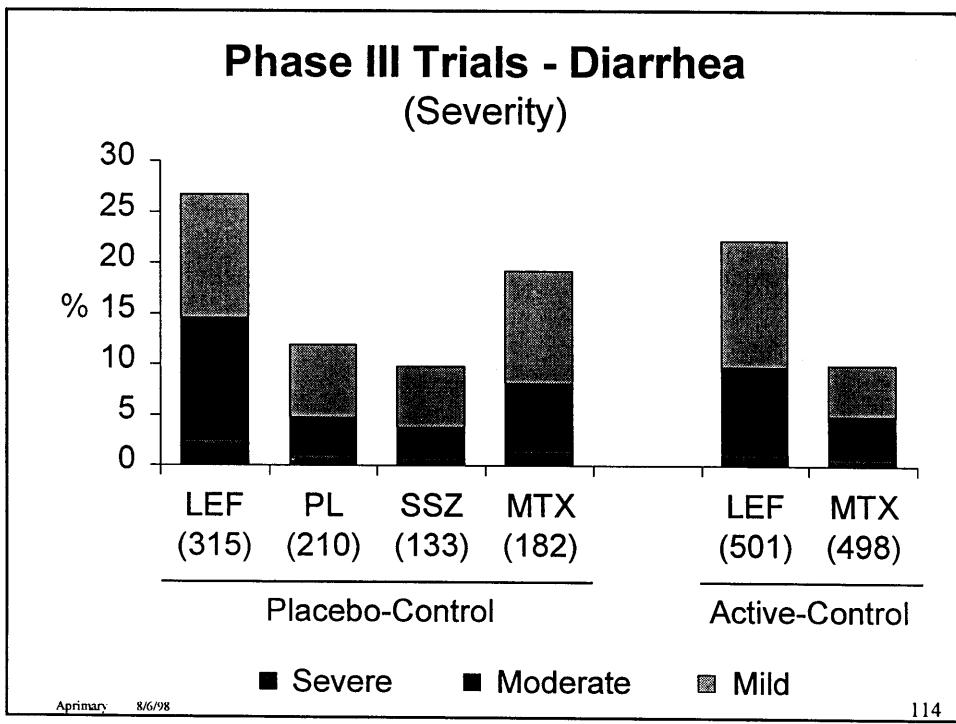
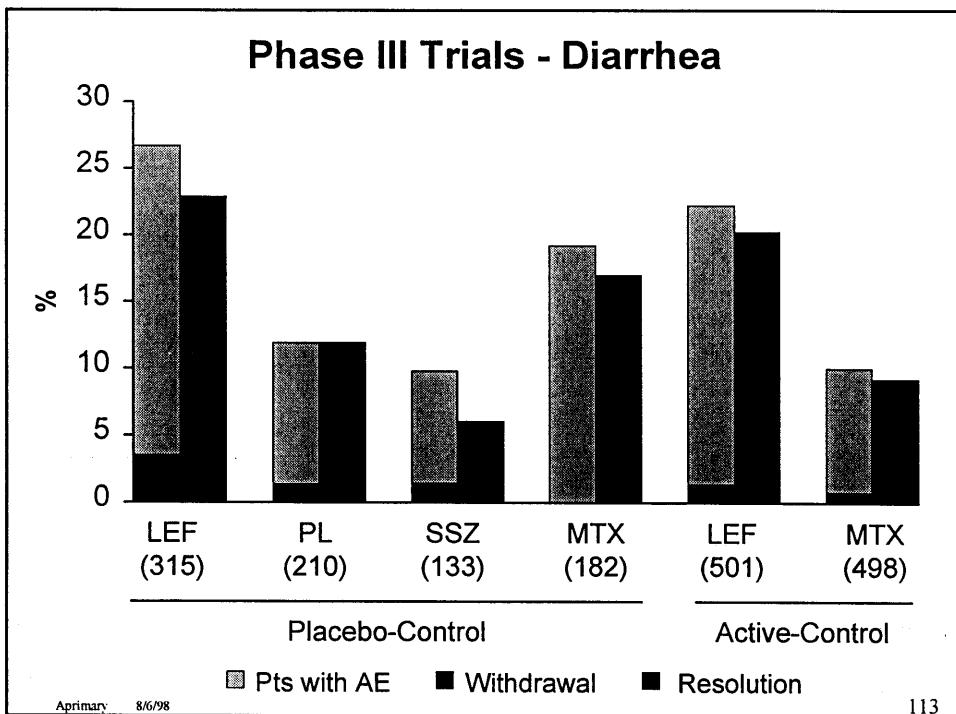
Gastrointestinal Adverse Events

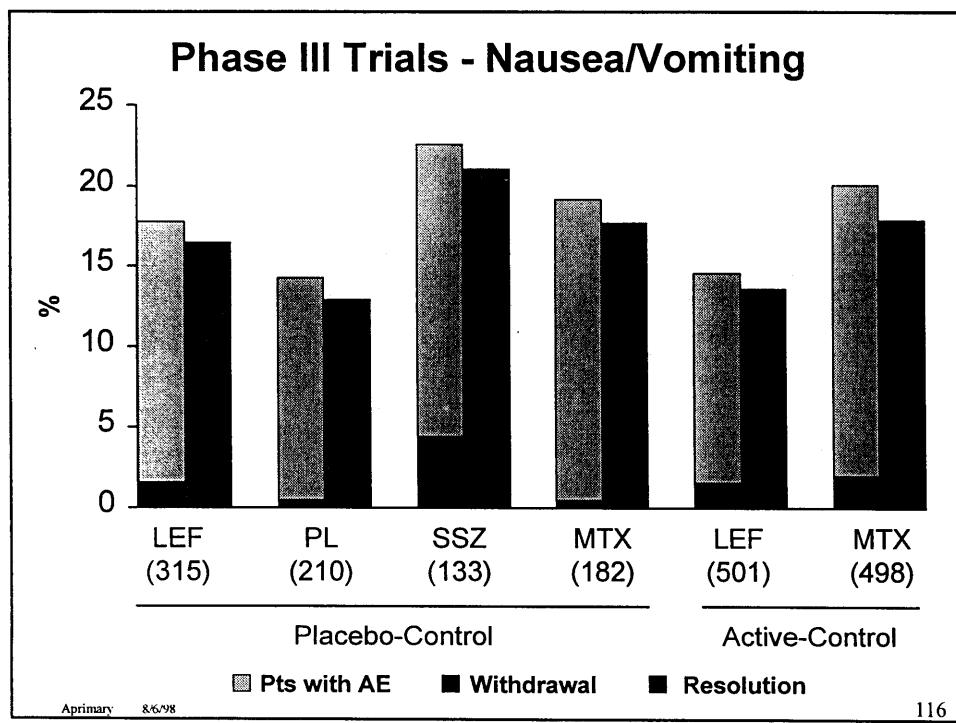
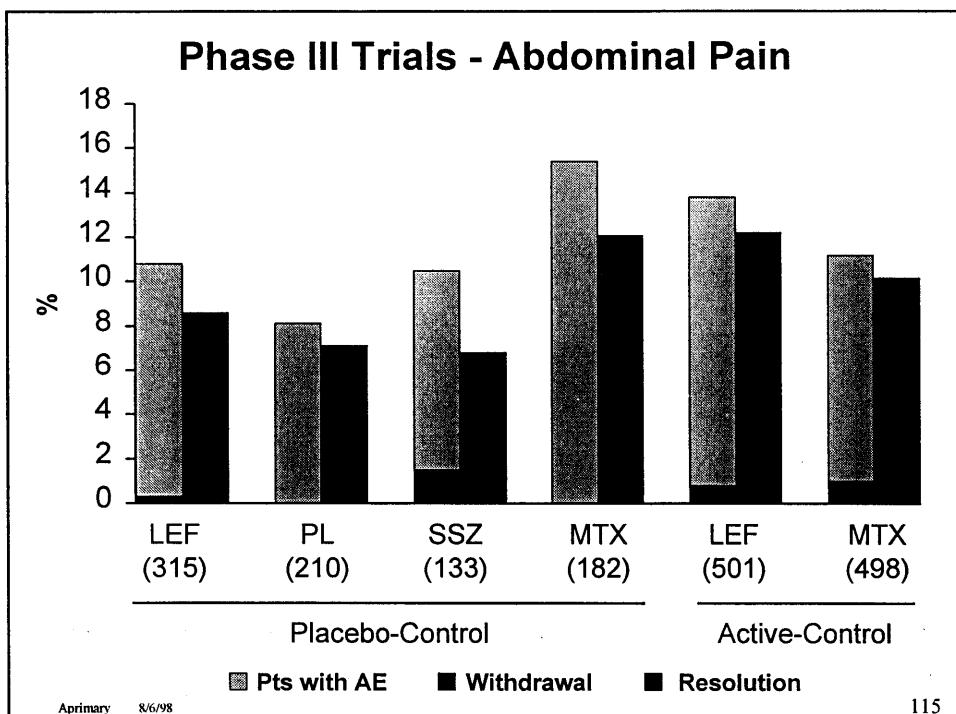
- Diarrhea
- Abdominal Pain
- Nausea and/or Vomiting
- Oral Manifestations

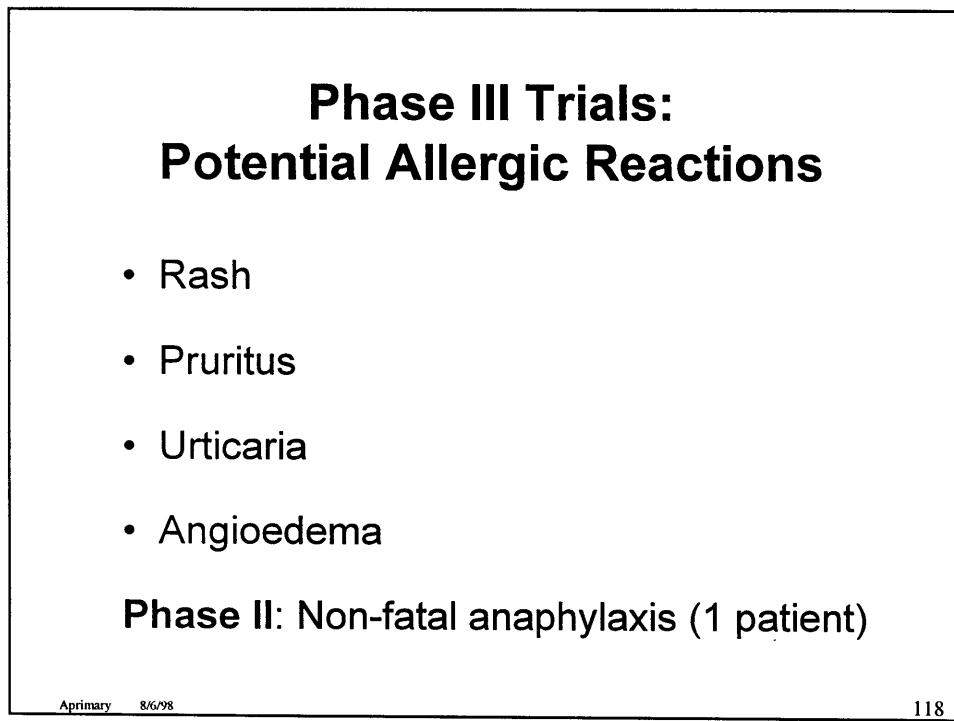
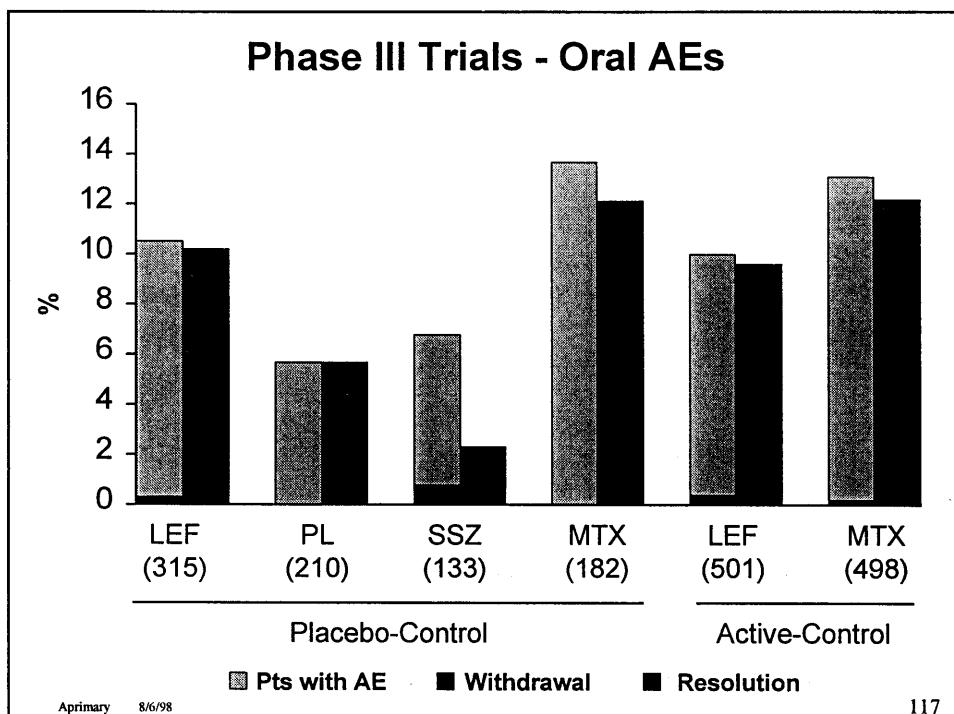
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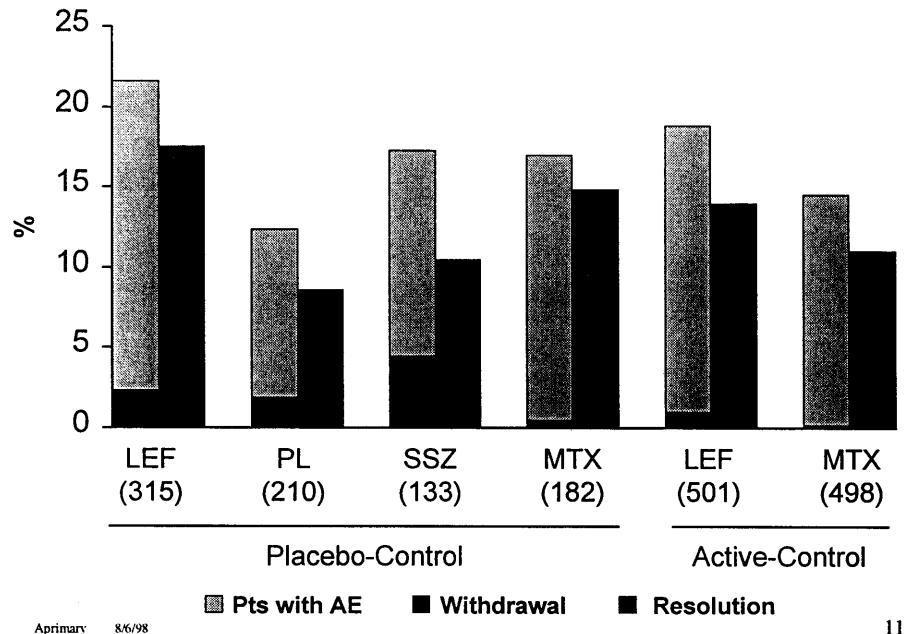








Phase III Trials - Potential Allergic Reactions



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Phase III Trials - Infections

- Upper respiratory tract infection
- Bronchitis
- Pharyngitis
- Flu syndrome
- Pneumonia
- Cystitis

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Phase III Trials - Infections (%)

	Placebo-Control				Active-Control	
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)
Total Pts With AE	44.4	38.6	37.6	59.9	46.9	47.6
SAE	2.9	1.0	1.5	1.1	3.6	3.0
Withdrawals	1.6	1.0	1.5	1.1	1.8	1.6
H. simplex/zoster	1.6	0.5	3.8	6.6	4.0	4.2
Sepsis	0.3	0.5	1.5	0.5	0	0
Opportunistic infec.	0	0	0	0	0	0
Mean duration (days)	19.0	16.7	16.4	19.1	25.8	25.7

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Phase III Trials - Hypertension (%)

	Placebo-Control				Active-Control	
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)
Total Pts With AEs	8.9	4.3	3.8	2.7	9.8	4.0
SAE	0.6	0.5	0	0	0.4	0.2
Withdrawals	0.6	1.0	0	0	0.6	0.2
Pre-existing HTN	7.3	3.8	3.0	1.1	8.0	3.6
New Onset HTN	1.6	0.5	0.8	1.6	1.8	0.4
Conc NSAIDs	1.3	0	0	1.6	1.6	0.4
Conc Corticosteroids	1.0	0.5	0	1.1	1.2	0.4

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Phase III Trials - Reversible Alopecia (%)

	Placebo-Control				Active-Control	
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)
Total Pts With AE	8.9	1.4	6.0	6.0	16.2	9.8
SAE	0	0	0	0	0	0
Withdrawals	0.3	0.5	0	1.1	1.4	0.2
Resolved	4.8	1.0	4.5	2.2	10.6	3.2

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Safety Results

- Exposure
- Adverse Events
- **Serious Adverse Events**
- Laboratory
- Summary

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Overall Summary of Adverse Events (%)

	Placebo-Control				Active-Control	
	LEF (315)	PL (210)	SSZ (133)	MTX (182)	LEF (501)	MTX (498)
Patients with AE	92.4	82.9	91.0	91.8	94.0	93.6
Withdrawals	18.1	7.1	22.6	10.4	18.8	15.1
Patients with SAE	15.9	11.4	16.5	8.2	31.1	27.3
Related	2.9	3.3	8.3	2.7	7.2	7.6
Withdrawals	4.4	2.9	4.5	2.7	7.6	5.4
Related	2.2	1.4	4.5	1.6	4.0	3.2

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All Clinical Trials - Deaths

	LEF	PL	SSZ	MTX	Total
Patient years	2077	226	258	936	
Deaths					
Total cases	20	2	3	20	45 *
Incidence/100 pt. yrs	0.96	0.88	1.16	2.14	

* 1 patient died during screening without study medication

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All Clinical Trials - Malignancies

	LEF	PL	SSZ	MTX	Total
Patient years	2077	226	258	936	
Malignancies					
Total cases	20	3	2	16	41
Incidence/100 pt. yrs	0.96	1.33	0.78	1.71	
Lymphoproliferative disease					
Total cases	3	0	1	1	5
Incidence/100 pt. yrs	0.14	0	0.39	0.11	

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All Clinical Trials - Rare Events

	LEF	PL	SSZ	MTX
Patient years	2077	226	258	936
Total cases:				
Interstitial pneumonitis	0	0	0	5
Renal failure	0	0	0	3
Agranulocytosis	0	0	2	0

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Safety Results

- Exposure
- Adverse Events
- Serious Adverse Events
- **Laboratory**
- Summary

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Clinical Laboratory Results

- Means
- Shifts
- Clinically Noteworthy/Contingency Tables
- Adverse Events

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Leflunomide: Hematology

No Effect	No Clinically Significant Effect
Hb/Hct	Neutrophils
Lymphocytes	Platelets
Monocytes	Eosinophils
Basophils	

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Phase III Trials Leflunomide: Hematology

- Hb/Hct:
 - No treatment related anemia
 - Increases in ACR responders
- WBC:
 - No sustained leukopenia (WBC < 2,000/ μ l; 1 case of neutropenia in alternate therapy of 301US)
- Platelets:
 - No sustained thrombocytopenia (platelets < 100,000/ μ l)

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Leflunomide: Chemistry

No Effect	No Clinically Significant Effect	Potential Clinical Effect
Sodium	Potassium	Uric Acid
Chloride	Calcium	ALT/AST
Bicarbonate	Phosphorous	
Creatinine/BUN	Alk. Phosphatase	
Tot. Prot./Albumin	CK	
Total Bilirubin	Cholesterol	
Glucose	Triglycerides	

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Proximal Tubule Effect: 301US

Patients (%) With Value < LLN During Rx	LEF (182)	PL (118)	MTX (182)
Uric acid	31.3	5.9	4.4
Uric acid and calcium	7.7	0	1.1
Uric acid, calcium, and phosphorus	1.6	0	0.5
Uric acid, calcium, phosphorus, and bicarbonate	0	0	0

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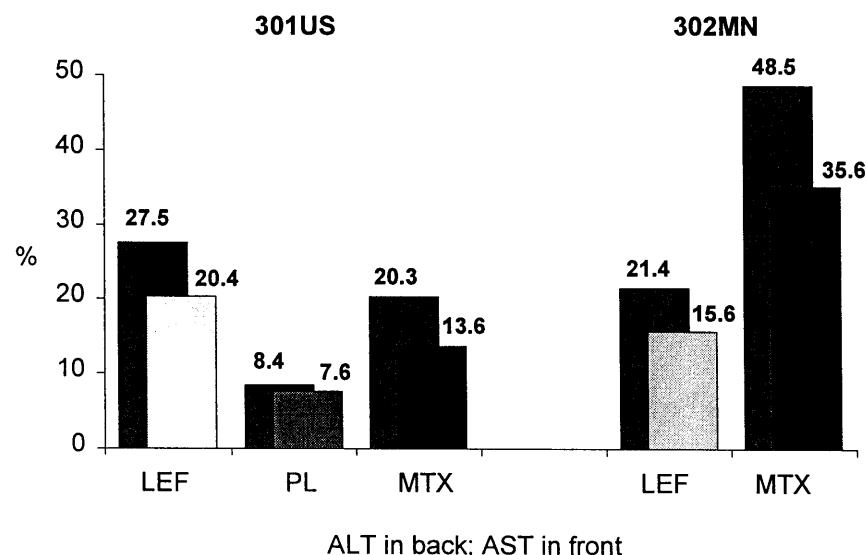
Liver Function Tests

Results will be shown for each study

Reasons:

- Different treatment duration
- Different folate supplementation
- Different monitoring

AST and ALT Elevations



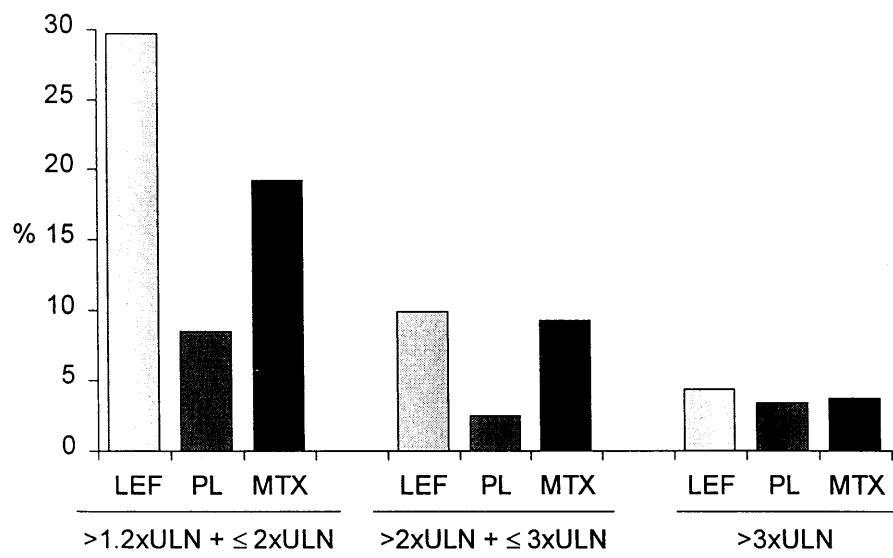
Summary of LFT Elevations (%)

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
Reported AEs	14.8	2.5	11.5	3.8	2.2	2.3	5.8	16.9
SAEs	1.1	0.8	1.1	0	0	0.8	0.2	0.6
Withdrawals	7.1	1.7	4.4	0.8	1.1	1.5	1.6	3.2

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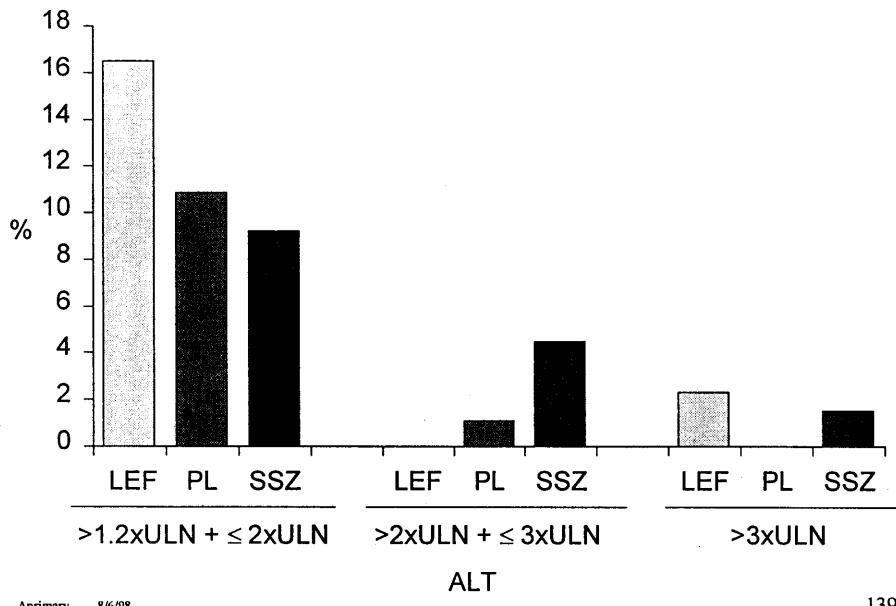
LFT Elevations: 301US



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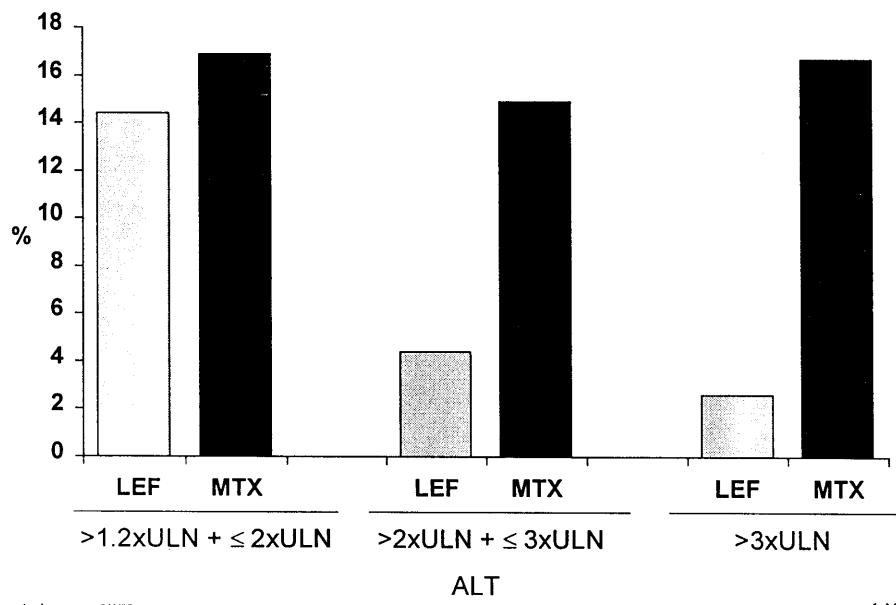
LFT Elevations: 301MN



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LFT Elevations: 302MN



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Reversibility of ALT Elevations

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
ALT								
>2 and ≤3x ULN								
(%)	6.6	0	6.6	0.8	0	4.5	4.4	14.9
Reversed to								
≤2 x ULN	6.6	-	6.0	0.8	-	3.8	4.0	14.0
>3x ULN	4.4	2.5	2.7	1.5	1.1	1.5	2.6	16.7
Reversed to								
≤2x ULN	4.4	2.5	2.7	1.5	1.1	1.5	2.4	16.5
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Timing of ALT Elevations (>2 and ≤3x ULN)

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
%								
%	6.6	0	6.6	0.8	0	4.5	4.4	14.9
N	12		12	1		6	22	74
Months								
0-3	6	-	6	1	-	5	11	16
4-6	4	-	3	-	-	1	4	22
7-9	2	-	2	-	-	-	2	19
10-12	-	-	1	-	-	-	5	17
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Timing of ALT Elevations (>3x ULN)

	301US			301MN			302MN	
	LEF (182)	PL (118)	MTX (182)	LEF (133)	PL (92)	SSZ (133)	LEF (501)	MTX (498)
%	4.4	2.5	2.7	1.5	1.1	1.5	2.6	16.7
N	8	3	5	2	1	2	13	83
Months								
0-3	6	1	1	2	1	2	7	27
4-6	1	1	3	-	-	-	1	34
7-9	1	1	1	-	-	-	-	16
10-12	-	-	-	-	-	-	5	6

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Liver Biopsies per ACR Guidelines

301US

#1- LEF: post 106 weeks Rx: Roegnik IIIA

USF01: Combination MTX+LEF

#2 - post 58 weeks Rx: Roegnik I

#3 - post 60 weeks Rx: Roegnik IIIA

#4 - post 60 weeks Rx: Roegnik IIIA

Safety Results

- Exposure
- Adverse Events
- Serious Adverse Events
- Laboratory
- Summary

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Phase III Trials - Safety

- Adverse events associated with Leflunomide treatment include
 - Gastrointestinal symptoms
 - Allergic reactions
 - Alopecia
 - Elevated LFTs
- They
 - Are generally mild to moderate in severity
 - Respond to supportive treatment
 - Resolve without sequelae

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Phase III Trials - Safety

- LFT elevations are usually asymptomatic and reversible
- AST and ALT should be monitored during treatment
 - ALT more than once > 2xULN
→ dose reduction to 10 mg/day
 - ALT more than once > 3xULN
→ discontinuation
- Although data are limited to date, there is no evidence to suggest Leflunomide treatment is associated with clinically serious liver disease

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Phase III Trials - Safety (Cont'd)

- The tolerability profile of Leflunomide treatment in active RA is acceptable in this population
- Leflunomide treatment appears not to result in
 - agranulocytosis
 - thrombocytopenia
 - renal failure
 - interstitial pneumonitis

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Agenda

- Introduction - Elaine Waller, PharmD
- Preclinical and Pharmacokinetic Data
 - Mark Eller, PhD
- Clinical Efficacy Data - Vibeke Strand, MD
- Clinical Safety Data - Iris Loew-Friedrich, MD
- **Clinical Evaluation of Arava**
 - Marc Hochberg, MD
- Conclusion - Elaine Waller, PharmD

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Management of Rheumatoid Arthritis

- Current
 - Single agents
 - Combination therapies
- On the horizon
 - New chemical agents
 - New biologic therapies

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Management of RA

Limitations of Currently Available DMARDs

- May not prevent progression of joint damage despite apparent clinical response/control
- May not be tolerated due to toxicity
- Delayed onset of action
- May not have prolonged efficacy

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Management of Rheumatoid Arthritis

- Current
 - Single agents
 - Combination therapies
- On the horizon
 - New chemical agents
 - New biologic therapies

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Leflunomide

- Novel agent for the treatment of patients with rheumatoid arthritis
- Unique mechanism of action
 - Reversible *de novo* pyrimidine synthesis inhibitor
- Immunomodulatory agent
 - Inhibition of animal models of RA, other autoimmune diseases and GvHD

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Evaluation of Pivotal Studies

- Data are derived from 12 month PBO- and active comparator-controlled studies with “state of the art” x-ray and physical function/HRQOL assessments
- Results with leflunomide are robust and consistent across studies
- Improvements are clinically meaningful

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Efficacy: Summary

- Significantly superior to placebo in ACR Response and all individual clinical and laboratory measures of disease activity/severity in both trials
- Comparable to both methotrexate and sulfasalazine

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Efficacy: Summary (Cont'd)

- Significantly reduces the rate of progression of radiologic changes of RA, including erosions and joint space narrowing
- Significantly improves functional limitation and health-related quality of life

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Safety: Summary

- Data on over 1100 patients in controlled trials
 - Over 2000 patient-years of therapy
 - 63% treated for more than 1 year
- Dropout rate for adverse events 15-20%
 - Comparable to methotrexate
 - Less than sulfasalazine

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Safety: Summary (Cont'd)

- Common adverse reactions
 - GI symptoms
 - Alopecia
 - Allergic reactions
 - Elevated transaminases
- No episodes of agranulocytosis, severe thrombocytopenia, interstitial pneumonitis, acute renal failure or opportunistic infections

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DMARDs in the Management of RA

Considerations

- Rheumatologist's estimate of disease severity and prognosis
- Convenience of administration
- Efficacy and toxicity
- Cost of therapy

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Management of RA

Features of Leflunomide

- Slows progression of joint damage in addition to providing clinically meaningful response
- Well tolerated
- Onset of response evident by 4 weeks; mean time to ACR response 8-10 weeks
- Sustained efficacy

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Leflunomide: Use in Management of RA

- First line therapy in patients with moderate-to-severe active disease and/or a poor prognosis
- Use after hydroxychloroquine in patients with mild disease and/or a good prognosis
- Can be used in combination with methotrexate

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Agenda

- Introduction - Elaine Waller, PharmD
- Preclinical and Pharmacokinetic Data
 - Mark Eller, PhD
- Clinical Efficacy Data - Vibeke Strand, MD
- Clinical Safety Data - Iris Loew-Friedrich, MD
- Clinical Evaluation of Arava
 - Marc Hochberg, MD
- Conclusion - **Elaine Waller, PharmD**

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ARAVA

- Novel immunomodulatory agent
- Treatment of active rheumatoid arthritis to:
 - Improve signs and symptoms
 - Retard joint destruction
 - Improve function
 - Improve health-related quality of life

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Academia

- Robert Brent, MD, PhD
Thomas Jefferson University
Jefferson Medical College
- Gabriel Garcia, MD
Stanford Health Services
- Onsi Kamel, MD
Southern Illinois University
School of Medicine
- John Sharp, MD
Emory School of Medicine
- Andrew Whelton, MD
Johns Hopkins University

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